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OF THE CHILDREN'S HOSPITAL

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Problems of the Central Nervous System Simulating Cerebral Palsy*

Colonel Ogden C. Bruton, MC†
Captain Billy F. Andrews, MC‡
Captain Wendell P. Searer, MC§
Captain Stuart J. Danoff, MC¶

Dr. Bruton:

Many of us feel that the next advance in medicine could well be in the area of cellular metabolism as it relates to the various known and unknown enzymatic systems. Pathological conditions resulting from abnormal enzymatic processes present challenging problems in the area of intermediary or intracellular metabolism.[1] As clinicians we can all think immediately of many of these syndromes. Many have people's names attached and are rare in their gross form but are possibly common if each syndrome or disease spectrum could be recognized in its entirety. Since the pathologist helps us not at all and tells us only what the end result is, we must challenge the biochemist to break the ring of the unknown surrounding these problems, which would seem to be almost endless in their scope.

Figure 1 demonstrates a potential disease spectrum. The upper half of the diagram represents normal intracellular metabolism, and the lower half the deranged or imbalanced intracellular metabolism. The right lower quadrant represents what may occur in the typical case of Niemann-Pick disease, in which the infant is expected to expire following mental and physical debility with gross changes in many organs due to intracellular deposition or accumulation of abnormally large amounts of sphingomyelin. The left lower quadrant is a schematic representation, if you will, of many such processes; in these, however, the imbalance is not complete and results in a more prolonged disease with a more insidious onset or with

* From the meeting of the Combined Pediatric Centers of the Greater Washington Area, presented by the Department of Pediatrics, Walter Reed Army Hospital, May 28, 1959.

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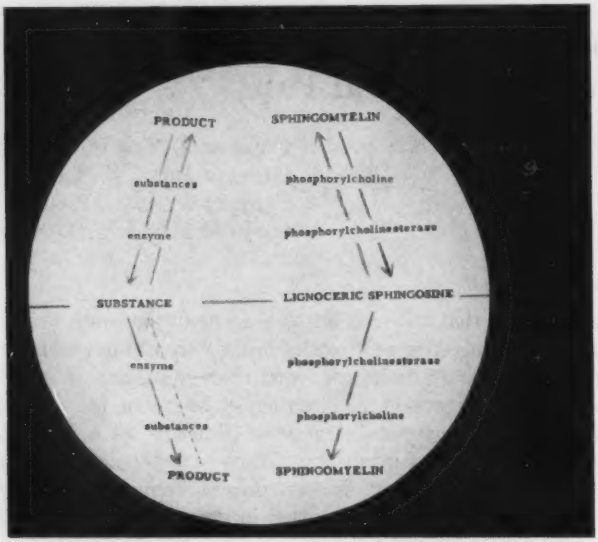

FIG. 1. Schema of intracellular metabolism: normal and imbalanced

delayed clinical manifestations. Such may be the situation in adult or chronic Gaucher's disease as compared to the more acute Gaucher's disease of infancy. Certainly this concept appears to apply to the following child with Niemann-Pick disease presenting as a rare and unusual clinical picture.

CASE 1

This 6 year old Caucasian girl of Irish-American ancestry was admitted to our hospital in July 1958 after prolonged and extensive study at a leading university medical center because her kindergarten teachers complained of her inattentiveness, immaturity and slowness. No known abnormalities were admitted in her ancestors or their offspring in three preceding generations, and one male sibling, age 7 years, was said to be normal. There was no known Jewish blood on either side of the family. The mother thought the pregnancy and birth were normal. The child's early mental and physical development was quite satisfactory; she sat alone at 6 months of age and walked at 14 months. In retrospect, only the mother was aware of the insidious onset of awkwardness and bizarre behavior which started about 3½ years of age and had progressed so that the child fell daily and often acted as if she were drunk. In telling a story she rapidly jumped from one story to another, and her only satisfaction seemed to come from singing, dancing and playing records.

The referring hospital reported the physical examination to reveal an extremely uncooperative child with a clumsy slapping gait who was unable to perform any fine, coordinated movement. A large mass in the left upper abdomen was thought to be either kidney or spleen. Complete genitourinary, gastrointestinal, and eye, ear,

FIG. 2. Case 1: Patient showing enlarged spleen and normal nutrition

nose and throat investigations were reported normal. An electroencephalogram, x-rays of the skull, blood cholesterol and x-rays for bone age were normal. Psychological evaluation estimated that she was functioning in the average range intellectually but was disturbed emotionally and was not in complete contact with reality. The final impression was that she represented either a case of juvenile schizophrenia or some congenital central nervous system disease with cerebellar involvement.

When we examined her, she was noted to cry and laugh without apparent reason, had moderate difficulty walking, and was incoordinated in her play. She was not withdrawn and greeted everyone with an incoordinated salute as she shouted, "Attention." She was fairly well nourished and developed, and except for her large spleen (fig. 2), other significant findings related to the neurological examination which was also surprisingly normal except for her incoordination. There was no cherry red spot seen in either ocular fundus, and the funduscopic examination was otherwise normal.

The total blood lipid value was 600 mg. per 100 ml., and the blood cholesterol was 100 mg. per 100 ml. Needle biopsy revealed normal liver tissue. Bone marrow needle biopsy revealed large foamy cells measuring 40 to 50 μ in diameter and containing finely vacuolated cytoplasm and eccentrically placed vesicular nuclei. Various stains failed to identify the exact nature of these cells. Cells obtained from the spleen by needle biopsy were identical with those observed in the bone marrow (fig. 3). However, chemical identification could not be determined and the observed histiocytosis permitted no clinical correlation with known entities.

The child's spleen was surgically removed and chemical analysis of the splenic tissue in two laboratories gave results consistent with those found in Niemann-

FIG. 3. Case 1: Section of spleen, showing large "storage" cells

	PER CENT OF:	LAB NO. 1	LAB NO. 2	NORMAL AVERAGE
TOTAL LIPIDS	FRESH WT.	10.37	7.35	2.68
CEREBROSIDE	TOTAL LIPIDS	4.97	--	0.94
GLYCOLIPID	TOTAL LIPIDS	4.10	4.55	1.26
CHOLESTEROL	TOTAL LIPIDS	16.0	--	4.22
PHOSPHATIDE	TOTAL LIPIDS	55.3	44.9	42.68
SPHINGOMYELIN	PHOSPHATIDE	55.0	49.2	19.96

FIG. 4. Case 1: Chemical analysis of spleen. (Courtesy of L. Lahut Uzman, M.D., Harvard Medical School, and Eberhard Trams, Ph.D., National Institutes of Health.)

Pick disease (fig. 4): 1) a high total lipid, and 2) an absolute increase in sphingomyelin.

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Dr. Andrews:

Initial description of the syndrome, progressive cerebellar ataxia and oculocutaneous telangiectasia, is attributed to Madam Louis-Bar in 1941.[1] A period of 16 years passed before other reports followed from various parts of the world. The frequent association of sinopulmonary infection was recognized and added as part of the syndrome.[2-5]

The presenting symptomatology, physical findings, and laboratory studies of the present case were similar to those described by other authors from California, Belgium, and the National Institutes of Health. It is of interest that 9 of 20 previously reported cases have come from California.[4] With the addition of this case, there are 21 known cases; 12 of the patients are girls and 9 boys. The average age at time of diagnosis was 11 years, with a range from 7½ to 25 years. The cases have involved 13 families and 7 pairs of siblings. Affected families have had about the same number of uninvolved children. It is therefore thought that the syndrome represents a heredofamilial disorder which is probably transmitted by a simple autosomal recessive gene.[4, 5] We found no evidence that the disease was heredofamilial in this case.

CASE 2

This 10 year old white boy was hospitalized for the first time at Walter Reed October 4, 1958 for evaluation of poor coordination. He was the result of a second and normal pregnancy, and there were no complications in the paranatal or neonatal periods. His birth weight was 7 pounds 2 ounces. He sat alone at 6 months of age, and at 12 months of age began to walk but was unsteady. He fell frequently and had a peculiar backward stepping, forward stepping, rocking gait. At 18 months of age, following examination at several university medical centers, the parents were told that he had a form of atypical cerebral palsy.

He began to speak simple words at about 12 months of age, and at about 2 years could form simple sentences. His toilet training was started at about 2 years of age and was said to have been completed at about 28 to 29 months. During the first two years of life he had repeated episodes of otitis media and upper respiratory tract infections. At 2½ years of age he had an adenoidectomy, after which he remained free of ear symptomatology. From that time to the age of 6 years his parents considered his progress to be satisfactory except for occasional falls and episodes of bronchitis. He started school at the age of 6 and did well except in penmanship. During his first year at school the parents noticed a peculiar reddening of his conjunctivae. He began to have some drooling and jerking movements of his head and shoulders at 7 years of age; however, he was still able to play baseball, to wrestle

and to run. At 8½ years he began to complain of jerking movements of his eyes which hindered his reading ability, and it was about this time that the mother noticed red spots in the creases of his neck and antecubital fossae although there was no increased bruisability or bleeding tendency. It was also quite apparent that the patient's coordination and gait were progressively worsening and that speech was becoming slurred.

During the 9 months prior to hospitalization at Walter Reed the child had progressive difficulty in feeding himself, writing, reading and walking; all of this necessitated his removal from public school. Despite these changes, no definite mental retardation or deterioration was noted, and he remained alert. He could watch television, read comic books and occasionally look at the newspaper. Respiratory infections continued, and the parents stated that he had at least two documented cases of bronchopneumonia a year between the ages of 6 and 10.

The father and mother at the time of his hospitalization were 42 and 40 years of age respectively. There was no history of consanguinity or of a similar disorder in other members of either of their families. A 14 year old sister is living and in excellent health. The mother gave a history of having had rheumatic fever, and had an allergic background. The maternal side of the family has numerous members with hay fever but none with asthma. A paternal grandfather had tuberculosis, and a great aunt had diabetes.

The patient's past history was significant in that he had received all of the immunizations that our military requires. He had never had any serum administered.

FIG. 5. Case 2: Note inability to stand alone and the sad masklike facies and drooling.

FIG. 6. Case 2: Telangiectasia of the ocular conjunctivae

His usual infections were treated with the tetracyclines, sulfas and penicillin, and he never had a known adverse reaction. A history of rubeola, rubella, mumps and varicella was obtained, and with these there were no complications.

Physical findings at this hospitalization revealed a well developed well nourished white boy who was alert and well oriented as to time and place. There was marked drooling and sad masklike facies (fig. 5) and athetoid movements of the entire body. It was noted that he could not stand without assistance. His weight was 66 pounds and his height 55 inches. Blood pressure, pulse and respirations were normal.

Figure 6 shows the horizontal appearing telangiectasia of his ocular conjunctivae. The pupils were equal in size and reacted to light and distance. In the left iris there was a 2 mm. brownish irregular pigmented area at 2 o'clock. The fundi were normal. There was a lateral fixed nystagmus with constant slow jerking movements of the eyes. The extraocular movements seemed to be within normal limits but were a little sluggish. The external ears also had telangiectasia, as illustrated in figure 7. These were found over the proximal attachment and also over the pinnae.

There was a yellow nasal discharge. Examination of the mucous membrane did not reveal vascular abnormalities. Areas of telangiectasia were also found on the folds of the neck, the antecubital folds (fig. 8) and the popliteal areas. There were no other skin lesions noted. The lungs and heart were normal to the usual methods of examination, and there were no abdominally palpable viscera.

Neurological examination revealed athetoid movements of both body and extremities and intention tremor of the extremities. His gait was ataxic, had a wide base and a slapping, high stepping appearance which seemed to be related to the extensor muscles. He could not walk or stand unassisted. The Romberg test could not be evaluated because the patient swayed equally well to either side. There was bilateral adiodokokinesis of the fingers. The bilateral facial weakness and minimal weakness of the arms and leg extensor muscle groups were noted; there was, however, no atrophy or spasticity of these muscles. Deep tendon reflexes were generally hypoactive, but superficial abdominal and cremasteric reflexes were present and normal. Pain, touch, temperature and vibratory senses were intact. There was no astereog-

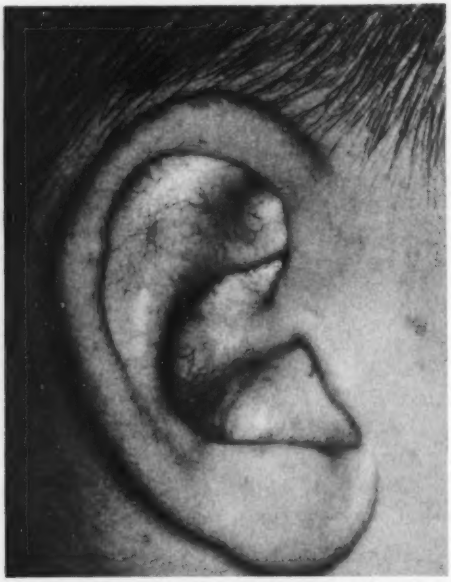

FIG. 7. Case 2: Telangiectasia of the external ears (pinna)

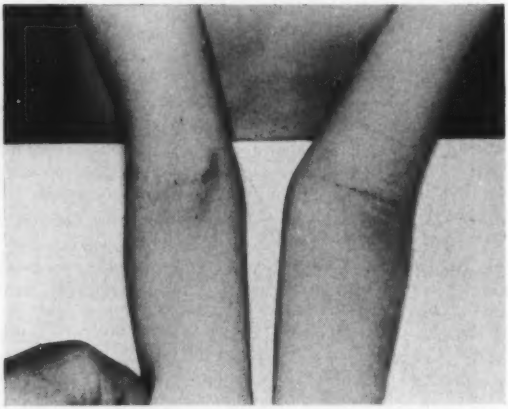

FIG. 8. Case 2: Telangiectasia of the antecubital folds

nosis. Plantar flexion occurred bilaterally; there was no clonus. Memory for past and recent events, ability to add, subtract and multiply, and comprehension appeared within normal limits.

Roentgenograms of the skull and chest were normal; electroencephalograms were

reported within normal limits. Examinations of the spinal fluid were normal. Urinalysis was normal, and the phenylpyruvic acid test was negative. Blood chemistries, liver function studies and thyroid studies were within normal limits. The total protein was 7 Gm. per 100 ml., serum albumin 4.4 Gm. per 100 ml. and serum globulin 2.6 Gm. per 100 ml. Serum protein electrophoresis revealed 8 per cent of the total protein to be gamma globulin, equivalent to a serum level of 560 mg. per 100 ml. Skin testing for tuberculosis was negative.

Since the patient's admission to the hospital he has also been studied at the National Institute of Neurological Diseases and Blindness. Tests for abnormal urinary amino acids, liver and thyroid function studies, and left common carotid arteriography were performed and all interpreted as normal. The low gamma globulin level was confirmed (total protein of 7.2 Gm. per 100 ml., 5 per cent of which was gamma globulin). When tested by the Weschler Intelligence Scale for Children he was found to have borderline intelligence. Presumably the low score is to be partly explained as a result of the physical restriction of the patient and his lack of opportunity to lead a normal life.

DISCUSSION

Progressive cerebellar ataxia with an average onset at 12 months of age is the first manifestation of this condition. Oculocutaneotelangiectasia has its average onset at 5 years; the conjunctivae are affected first, and then the ears, face and popliteal folds in order of succession. Sinopulmonary infections usually begin to occur from the first to the fourth year and can be documented with x-rays. Peculiar eye movements are then noted. These simulate ophthalmoplegia, and the patients are sometimes first seen by the ophthalmologist. There is usually a fixed nystagmus and a sad facies with drooling. All are said to have an equable disposition. Only Madam Louis-Bar's case is stated to have shown an actual mental deficiency, and this may have been because of the late stage of the disease and the physical impairment. Pneumonia is the usual terminating complication; this has occurred in patients from 9 to 25 years of age and may account in part for the scarcity of cases prior to the antibiotic era.

Studies of urinary content of amino acids and lead, and levels of serum copper and iron have been normal when performed. In only 2 cases of the entire group have protein electrophoresis revealed low gamma globulin levels; one of these was the present case. One other child also had a 5 per cent level of gamma globulin.

No abnormalities of the blood clotting mechanisms have been demonstrated. Electroencephalograms have always been interpreted as being within normal limits. Carotid arteriograms are either normal or show clumping of elements of dye in the smaller deep cerebral vessels. Pneumoencephalograms, when performed, have been normal or have revealed some degree of enlargement of the fourth ventricle and/or lateral ventricles.

Necropsy provides microscopic evidence of progressive, apparently primary, diffuse cortical cerebellar degeneration. There are enlarged venules

in the cerebellar leptomeninges and white matter. There is no significant change in the spinal cord.

A great number of diseases present with similar findings, but this syndrome has always been found to involve the skin and eyes. There have been those who have believed it to be one of the phakomatoses and have suggested that it should be a fifth member of the group which includes the cephaloretinalangiomatosis of von Hippel-Lindau, the cerebral angiomatosis of Sturge-Weber, the neurofibromatosis of von Recklinghausen and tuberosclerosis. The recently described Hartnup's disease in England may be a similar disease, but this has increased aminoaciduria, pellagra-like skin changes and mental deterioration.

It is postulated that a metabolic disturbance may be the basic defect in this syndrome. In other syndromes, the exact nature of which are unknown, clinical and pathological findings have first been described, followed later by biochemical investigation which reveals the basic defect in intracellular metabolism. At present, clinicians can do little save supply patients with this condition with antibiotics for their sinopulmonary infections, provide physical and occupational therapy for their psychological and neuromuscular needs, and stand by patiently and watch them deteriorate.

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Dr. Searer:

CASE 3

This 5½ year old boy was said by his mother to have had slow development since birth; this was particularly true of his speech development. He had had a convulsion at the age of 3½ years, followed by a progressive deterioration of balance, coordi-

nation and gait which had developed within a 6 month period, intermittent nervous twitching of the lips, and progressive inability to hear and see.

He was the product of a normal pregnancy and spontaneous delivery. Although all spheres of development were slow, this was especially true of his speech; he had failed to build up any appreciable vocabulary. Following his convulsion at age 3½ he was treated with dilantin and phenobarbital. Since that time he had had no real major convulsion but had had episodes of twitching of his lips and sometimes of his hands. At 4 years of age he began to lose his balance, his coordination became awkward, and his gait gradually deteriorated so that he became completely unable to walk by age 5. About the same time he lost his ability to chew any food. Until just prior to admission, he had responded to voice, but even this ability had decreased a great deal by the time we saw him. He did not follow objects with his eyes, and did not hold his head up well. The only cry he would make was when he was very hungry or in pain. He had stopped gaining weight and could eat only strained food. Constipation had been a real problem.

Past history revealed that he had been bruised by a car in 1957, just after the onset of the present illness.

Family history was significant in that one brother died of an illness very similar to the patient; death occurred at age 8 when the patient was 4½. The brother's illness was described as a progressive neuromuscular deterioration beginning at age 3, seizures at age 4 which continued until death, and gradually developing mutism and quadriplegia. He was autopsied at Walter Reed and a diagnosis of cerebral lipidosis was made. The parents were aged 29 and 27 years; there was no consanguinity and the family was not Jewish. The father's mother had died in an institution of an unknown mental disease at age 35.

Physical examination of the patient showed him to be 42 inches tall and 29½ pounds in weight. He was completely paralyzed. There was no response to auditory stimuli, and he also was apparently unable to see. There was a noticeable hypertrophy of the gums, the lips were chapped and cracked, and he had severe calculus of the teeth. The child was able only to utter an inarticulate cry from time to time; there were a few purposeless movements of the extremities, and he was apparently completely demented (fig. 9).

The corneal reflex was somewhat impaired, the gag reflex was intact; the tongue was protruded in the midline and appeared to be strong, but showed myoclonic twitches. Examination of his ocular fundi following mydriasis showed small red spots in the region of the macula and a definite pallor of the discs. There was a spastic quadriplegia, with flexion of the arms and wrists and adduction of the thumbs.

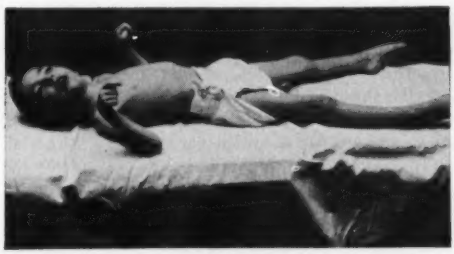

FIG. 9. Case 3: Spastic quadriplegia, blindness, and dementia

FIG. 10 Case 4: Dementia, spastic quadriplegia, amaurosis and deafness. Note similarity of appearance to younger brother (fig. 9).

The knees were flexed and the feet appeared clubbed. There was a tendency to flex the hips. Muscle tone was markedly increased. Following any tactile stimuli, myoclonic jerks could be observed in the arms and legs. There was a positive Babinski sign on the right and an equivocal one on the left.

Electroencephalogram showed a very abnormal background consisting of regular 3 to 5 per second slow waves of moderate high voltage distributed diffusely over both cerebral hemispheres. These were interrupted by bilateral synchronous shifting discharges, many of which were accompanied by myoclonic jerks of the limbs. An electroretinogram was done and showed evidence of macular changes and early optic atrophy suggesting degeneration of the deeper retinal layers compatible with a diagnosis of infantile amaurotic familial idiocy.

CASE 4

This 6½ year old boy (fig. 10) was the older brother of the patient of case 3 and the second of three children. He also had a history of slow neuromuscular development which was manifested especially in failure to develop speech until the age of 3. Generalized convulsions appeared at age 3½, followed by the development of stumbling gait and the deterioration of acquired speech to the point of complete mutism for the 18 months prior to admission. During this 18 month period, he gradually developed complete inability to walk as well as progressive incoordination, blindness and loss of hearing.

Physical examination on admission to this hospital was almost entirely identical to that of his younger brother. He could still turn to one side, but was unable to perform any other voluntary motion. There were frequent forceful tonic and sometimes clonic movements of all his extremities. In addition, there was evidence of dementia, spastic quadriplegia, amaurosis and deafness, as well as the red spots near the macula associated with optic atrophy.

Electroretinogram and electroencephalogram showed almost identical findings to those of his younger brother.

It was felt that, with the positive family history, the presence of symptoms between the ages of 2 and 3 years, clinical features characterized by myoclonus, mental retardation, blindness and spastic quadriplegia, together with the abnormal laboratory findings, a diagnosis of amaurotic familial idiocy of the late infantile type could be made.

DISCUSSION

Amaurotic familial idiocy, or Tay-Sachs disease, is one of the cerebromacular degenerative diseases.[1] It is characterized by idiocy, gradually

developing paralysis, and a cherry red spot in the macula. Associated findings are apathy, listlessness and blindness. The further course of the disease is characterized by rapid and progressive decline in physical condition, with death resulting from intercurrent infection occurring in the first year or two of life. It is thought to be hereditary, steadily progressive and always fatal. Typical cases are known to occur almost exclusively in Jewish children, but many exceptions have been reported.

The late infantile type of this disease, as described by Jansky and Bielschowsky, is quite rare. The main features are identical to those of the infantile type, with the exception of an older age of onset, slightly less fulminating course, and absence of a racial factor. Until the age of 3½ years, the child may appear normal physically and mentally and then show deterioration, develop convulsions and exhibit phenomena of decerebrate rigidity with accompanying bulbar signs. This condition would appear then to be another example of an enzymatic dysfunction which needs further elucidation by the biochemist.

REFERENCE

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COMMENT

Dr. Danoff:

These patients have not been presented as examples of rare or weird diseases to add to the list of case reports but rather as examples of biochemical experiments of nature which have produced disturbances in cerebral metabolism and therefore manifestations of widespread nervous system disease. A few years ago some of these patients were diagnosed as cerebral palsy or as mental defectives. Now we present them as separate clinical entities, and in the future, as the results of our biochemical investigations are realized, we will undoubtedly discover the specific enzymatic defects responsible for these conditions. It may then become possible to cure or else prevent them.

This concept is by no means a new one. Thirty odd years ago Garrod wrote a book entitled "Inborn Errors of Metabolism" in which he theorized that the absence of one enzyme could produce biochemical changes with widespread systemic manifestations.[1] One of his examples was alcaptonuria. Since that time, however, many diseases have been recognized as inborn errors of metabolism. A number of these involve the brain. It appears that when these enzymatic defects involve the basic substance of the human protoplasm, i.e., proteins, carbohydrates and lipids, they are more likely to produce aberrations in cerebral function.

To summarize a few of these and perhaps place our 3 cases in a different

TABLE 1

Cerebral Defects Associated with Disorder of Protein Metabolism

1. Phenylketonuria
2. Hartnup's Disease
3. Hepatolenticular Degeneration
4. Maple Sugar Urine Disease
5. Lowe's Disease
6. Argininosuccinic Acid Syndrome

perspective, we can consider those cerebral defects which are associated with diseases of metabolism of each of these substances. Of course the most classic member of the group of diseases associated with disorders of protein metabolism (table 1) is phenylketonuria, in which, as a result of an enzymatic defect in the conversion of phenylalanine to tyrosine,[2] there is a systemic reaction characterized by blonde hair, blue eyes, fair skin, a predisposition to eczema and mental deficiency. Hartnup's disease,[3] which is a recent addition to this group, is also characterized by an enzymatic defect which interferes with tryptophane metabolism and presents clinically not only with a pellagra-like rash and mental deterioration but also cerebellar ataxia. Hepatolenticular degeneration is perhaps due to a basic defect in ceruloplasmin metabolism.[4] Maple sugar urine disease is a new entity which is characterized by severe mental deterioration and a peculiar maple sugar odor to the urine. Amino acids in abnormal quantities have been found in the urine and serum of these patients,[5] and recently the basic biochemical defect has been postulated.[6] Lowe's disease[7] is another condition in which there is an abnormal aminoaciduria associated with mental deficiency, cataracts, glaucoma and osteoporosis. The newly discovered argininosuccinic aciduria syndrome[8] is also characterized by mental deficiency and an increased excretion in the urine of argininosuccinic acid. This list is by no means complete, and every month there are new additions to it.

Of the cerebral defects which are associated with carbohydrate metabolism (table 2), galactosemia is familiar to all pediatricians, and is, as we now know, due to absence of the enzyme phosphogalactoseuridyltransferase,[9] the enzyme which converts galactose-1-phosphate to glucose-

TABLE 2

Cerebral Defects Associated with Disorders of Carbohydrate Metabolism

1. Galactosemia
2. Idiopathic Hypoglycemia (?)
3. Sucrosuria
4. Gargoylism (Hurler-Pfaundler Disease)

TABLE 3

Cerebral Defects Associated with Disorders of Lipid Metabolism

1. Familial Amauroses (Tay-Sachs-Bielschowsky-Spielmeyer-Vogt Disease)
2. Niemann-Pick Disease
3. Infantile Gaucher's Disease
4. "Hsia's Disease"

1-phosphate. Clinically, galactosemia results in galactosuria, aminoaciduria, jaundice, hepatomegaly, cataracts, and mental deficiency. Idiopathic hypoglycemia is characterized by hypoglycemia and mental deficiency. There are those who believe that the mental deficiency in this condition is not due to hypoglycemia *per se*, since in other hypoglycemic conditions mental deficiency is not always constant.[10] Recently it has been demonstrated that such substances as casein or leucine can induce hypoglycemia in these patients.[11] Sucrosuria is another metabolic abnormality associated with mental deficiency,[12] and gargoylism has now been shown to be associated with an accumulation of a specific mucopolysaccharide in the cells of afflicted individuals.[13]

Cerebral defects associated with disorders of lipid metabolism[14] (table 3) are also part of this group of diseases. The familial amauroses, which are also known by a host of other names, are characterized by an accumulation of a ganglioside containing neuraminic acid in the cells of the brain. Niemann-Pick disease is associated with cerebral deposition of sphingomyelin. Infantile Gaucher's disease is also included in this group, as well as a recently described disease in which there is hepatomegaly, increased triglycerides, phospholipids and alpha-2 lipoproteins in the serum, and evidence of mental and physical retardation.[15]

What is the practical importance of this group of strange and exotic diseases? We believe that, in addition to furnishing certain basic biochemical information, these bizarre syndromes spotlight metabolic processes as being of truly fundamental consideration in every disease. We are excited and in anxious anticipation of what the future will reveal about such unknown entities as "cerebral palsy," "mongolism," "mental disease" and "mental deficiency."

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Clinical Pathological Conference

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PRESENTATION OF CASE

This 3 day old female infant was transferred to Children's Hospital from another hospital with a diagnosis of atelectasis neonatorum. The infant was full term, the product of a normal spontaneous delivery, and weighed

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7 pounds 12 ounces. Just after delivery, it was noted that she was cyanotic. She had a large amount of vernix caseosa in the nostrils, and laryngeal spasm was present. The material from her nose and mouth was suctioned and positive pressure oxygen was given. She improved, but four hours later again became cyanotic. She was again suctioned and given oxygen, and improved, but these periods of cyanosis and respiratory distress recurred several times. On the second day, she was fed water after which she vomited; all oral feedings were then stopped. Using a laryngoscope, a tube was passed into the trachea and a large amount of material aspirated, after which the infant improved.

Physical examination on the third day of life revealed a well developed, alert newborn in considerable respiratory distress, with retraction of the infracostal and supracostal spaces. The respiratory rate was 60 per minute. There was mucosanguineous material in the mouth. There was an absence of most of the pinna of the right ear. The breath sounds were bronchial in type, and many coarse rhonchi were heard. There was sinus tachycardia, but no other abnormality of the heart was noted.

The infant was given oxygen with Alevaire®, but there was no improvement in spite of frequent aspirations of the nasopharynx. Crystalline penicillin was given every 12 hours, and vitamin K was also administered. A portable chest x-ray was made on the following day. A second laryngoscopy was attempted but the infant expired during the procedure, 32 hours after admission, at approximately 5 days of age.

DISCUSSION

Dr. Delaney:

The portable chest x-ray (fig. 1) which I have just seen shows the bony structure, including the vertebrae, to be normal for a newborn. There is a large amount of air in the stomach and small intestine. The liver is seen to be about a centimeter above the iliac crest. The trachea is deviated to the right. There is a shift of the heart and mediastinum to the right, and atelectasis of the right apical region; there are increased vascular markings in the lower portions of the lungs. I see no abnormalities on the left side and I see no bowel in the chest.

This is a newborn with respiratory distress and cyanosis accompanied by a large amount of mucosanguineous material apparently coming from the respiratory tract. This gives us the wide differential of respiratory distress with cyanosis and we can start with central nervous system lesions. Intracranial hemorrhage in the newborn may take one of two forms. First, intraventricular hemorrhages are usually seen in prematures, but occasionally may be seen in older, full term babies with a history of trauma at birth. Apparently, however, this was a spontaneous delivery. Second, subdural hemorrhage may occur and is a cause of respiratory distress;

FIG. 1. Portable postero-anterior x-ray view of the chest. Note large amount of air in stomach and small intestine, enlarged liver, deviated trachea, shift of heart and mediastinum to the right and atelectasis of the right apical region.

frequently there may be convulsions, a bulging fontanel, and other more focal signs, as well as respiratory distress. However, the respiratory distress and cyanosis secondary to central nervous system lesions do not usually clear with suctioning of the upper respiratory tract. Anoxia can be the cause of central nervous system signs, and certainly the possibility in this patient must be thought of because the laryngospasm present at birth could have been a prime cause of anoxia.

Malformations of the lower jaws, epiglottis, and larynx must be considered; these are usually accompanied by much respiratory stridor, a symptom which is not mentioned. Elongation of the epiglottis is not usually severe enough to cause this amount of distress. Laryngeal webs or duplication of the vocal cords also do not cause this much distress in the newborn period and usually do not cause the infant's demise.

Pulmonary lesions capable of causing this infant's symptoms include: congenital malformations of the respiratory tract, pulmonary hyaline

membrane disease, bronchopneumonia of the newborn, pneumothorax, pneumomediastinum, and pulmonary hemorrhage. Congenital malformations of the pulmonary tract which might cause such severe symptoms are pulmonary hypoplasia (or pulmonary agenesis) and lobar emphysema. Pulmonary hypoplasia or agenesis occurs in males twice as frequently as in females and is usually accompanied by other congenital anomalies such as anencephaly, bilateral adrenal agenesis and polycystic kidneys. Potter's syndrome is a syndrome which includes bilateral renal agenesis, absence of the cartilage of the ear, low-set ears, and a broad face with a flattened nose and wide-spaced orbits. If present, these findings should have been noted during the physical examination. This child had an absent right external ear, and my renal disease consultant tells me that when the right ear is absent, then only the right kidney would be absent. This diagnosis, then, remains a possibility: pulmonary hypoplasia on the right with the mediastinal shift seen on x-ray, absence of the right ear, and renal agenesis on the right.

Pulmonary hyaline membrane disease is primarily a disease of newborns. It has a number of synonyms such as neonatal aphyxia, paranatal distress syndrome, and abnormal pulmonary ventilation syndrome. This condition is usually not present at birth, but comes on a few hours after birth and is seen more commonly in prematures, those infants born by Caesarian section, and those of diabetic mothers. This child was in distress apparently from the onset, and although she improved, I question the amount of the improvement. There is not this amount of mucosanguineous material accompanying pulmonary hyaline membrane disease which is usually described as an expiratory type of disease in which there is prolonged expiration and grunting comparable to what we see in older infants with bronchiolitis. The infant with hyaline membrane disease does well for a few hours, but then goes into respiratory distress and becomes cyanotic. Those infants I have seen, if they lived until the fourth day, usually improved and recovered. However, this is a pathologic diagnosis in which the pathologic findings of atelectasis, congestion and an eosin-staining intra-alveolar membrane are present. I do not think this infant had hyaline membrane disease, and believe that if there was a hyaline membrane, it may have been secondary to aspiration due to her original disease.

Pneumonia of the newborn occurs as a bronchopneumonia and is carried as a cause of death by the Bureau of Statistics. Whether this occurs intranatally or immediately after delivery I think is a matter of question. However, if it does occur intranatally, the infants apparently do well at first and become distressed some time after birth; the organism is usually *E. coli* or staphylococcus. In this condition, there is usually a history of ruptured membranes about 24 hours prior to delivery; we have no history

of that here. Other infections of the newborn period which should be considered include pulmonary or myocardial infections due to the Coxsackie virus. These infants are usually normal at birth, but the onset of the viral disease occurs shortly thereafter; if the infant does not die of the pulmonary disease, he may die at about four days of age of myocardial disease.

Pneumothorax and pneumomediastinum usually result from injudicious attempts at resuscitation. When laryngospasm is present, resuscitative measures may be too vigorous. These conditions are possibilities, but would probably be evident both on x-ray and physical examination. Pulmonary hemorrhage I mention only because there was mucosanguineous material aspirated from the mouth. Pulmonary hemorrhage is usually secondary to fetal anoxia, a condition for which the requirements are met in this infant at birth. With pulmonary hemorrhage, there is usually the same type of frothy mucosanguineous material that is seen with pulmonary edema or with severe congestive heart failure in the newborn period.

Other lesions, including congenital malformation of the heart and the great vessels, can cause respiratory distress and cyanosis in the newborn infant. A vascular ring is a possibility. This is usually associated with cyanosis following swallowing, but respiratory distress may or may not be present. Diaphragmatic hernia is another diagnosis which should be entertained; this may be extensive or mild, and present with symptoms of varying severity. The x-ray does not give any evidence of diaphragmatic hernia and the diaphragm is apparently in the normal position. Moreover, the respiratory distress and cyanosis of heart disease or diaphragmatic hernia does not clear with suctioning.

Esophageal atresia with tracheoesophageal fistula can present with this clinical picture. Apparently, just after delivery the infant was cyanotic and needed aspiration. We see this very frequently in newborns; however, this infant needed more than that: she needed positive pressure oxygen for respiratory distress. Four hours later she again became cyanotic; we can account for this by her aspiration of mucus and saliva. Following this, she vomited immediately after all feedings and needed laryngoscopic examination. During the process of laryngoscopy, she was suctioned out, and a large amount of material was aspirated, resulting in improvement in her condition. This condition could give us the roentgenographic picture of atelectasis and increased bronchovascular markings in the right lower pulmonary tract.

Therefore, for my first diagnosis, I am going to pick tracheoesophageal fistula, and wish to rule out pulmonary hypoplasia or agenesis on the right accompanied by renal agenesis and the absence of the right ear as my second diagnosis.

Dr. LoPresti:

As an added possible diagnosis we might consider duplication of the gastrointestinal tract which can occur anywhere from the base of the tongue to the anus. The majority occur in the ileocecal region, but those which occur at the base of the tongue cause severe inspiratory stridor and marked respiratory distress, and are frequently unrecognized. Such a complication may be ruled out by taking a little piece of gauze, grasping the infant's tongue and pulling it forward; if a tongue blade is then used to further depress the tongue, a cystic duplication at the base of the tongue is easily visualized.

Dr. Delaney has pointed out the relationship of renal anomalies with anomalies of the ear, but this gains extra importance since it gives rise to the definite possibility that the patient might have had another anomaly which caused her death. Anomalies of the ear are sometimes associated with congenital heart disease, and certainly one anomaly adds to the possibility of another.

The Pierre-Robin syndrome should perhaps be considered. This would occur in an infant who has a hypoplasia of the mandible (an Andy Gump type of chin), a cleft palate, and in about 50 per cent of cases, an anomaly of the central nervous system. Death from respiratory insufficiency occurs.

Pulmonary agenesis may be partial or complete, is usually on the right side, occurs predominantly in males, and in many instances is associated with hemivertebrae. The important thing about infants with pulmonary agenesis is that they do not die. It is amazing how much pulmonary agenesis infants can have and still have very little in the way of symptomatology. These points are against a diagnosis of pulmonary agenesis.

This child was having respiratory difficulty, and had a complete atelectasis of her right upper lobe as well as probable patches of atelectasis throughout the remaining lung. In a newborn infant who has a right upper lobe atelectasis we should immediately think of aspiration because this is the lobe that is most frequently involved in aspiration either of food or mucus. Another diagnosis which should be kept in mind when atelectasis of the right upper lobe is present is fibrocystic disease of the pancreas which also may present with such a finding.

The garden variety of tracheoesophageal fistula is one in which there is a blind upper esophageal pouch accompanied by a lower tracheal fistula of varying size which communicates with the stomach. It is easy to see how this blind pouch, if unrecognized, would fill up with mucus and saliva, and that this mucus would overflow into the trachea and throughout the lungs, and cause pulmonary difficulty. In addition, the first time an infant with this anomaly is fed, much of the formula will be aspirated.

It is important that this condition be recognized early. Of course the

simplest thing that a pediatrician can do is to attempt to pass a tube into the stomach. When the tube reaches the end of the blind upper pouch it will progress no further. However, I have seen a tube passed in an infant with tracheoesophageal fistula that instead of going into the blind pouch went down the trachea through the fistula and then into the stomach.

Dr. Rice:

It appears from the hospital chart that the diagnosis of tracheoesophageal fistula was not seriously considered during life. When we opened the thorax we found that the first portion of the esophagus ended blindly 1 cm. above the carina. The lower portion had its origin about 1 cm. below this, at the bifurcation of the trachea, the opening measuring 0.4 cm. in diameter. This segment emptied normally into the stomach. This is the most common form of tracheoesophageal fistula and occurs in about 90 per cent of all cases. The lungs were red and noncrepitant and weighed four times the normal. Microscopic examination revealed an aspiration type of pneumonia. A Meckel's diverticulum was found 37 cm. above the cecum. The pinna of the right ear was small, thickened and attached to the scalp. Subcutaneous edema was present.

The final pathological diagnoses were esophageal atresia; tracheoesophageal fistula; atelectasis and aspiration bronchopneumonia, bilateral; Meckel's diverticulum; and malformation of the pinna of the right ear.

The finding of the Meckel's diverticulum and the malformation of the pinna of the ear were not unexpected. Stephens et al.[1] and Gross[2] give almost identical percentages concerning the frequency with which other congenital anomalies can be expected to be found in this group of patients, viz., 33 per cent. Many of these infants are premature, the figures given by the above authors being 21 to 22 per cent. Humphreys et al.[3] state that 28 per cent of their cases were premature or had serious associated anomalies which were sufficient to prevent a successful surgical outcome. They found that the various anomalies were divided almost equally between the heart and the great vessels and the gastrointestinal and genitourinary tracts, with a smaller number being found in the central nervous system. Anomalous origins and abnormal courses of blood vessels in the neck are sometimes responsible for narrowing or atresia of the esophagus.

Years ago we adopted a do-nothing attitude when the diagnosis of esophageal atresia and tracheoesophageal fistula was infrequently made during life. Now that we are alert to the situation and have the ability to recognize it within 24 hours, we can have the assurance that if we can turn the patient over to a competent surgeon promptly and in good condition, a successful outcome can be expected in from 75 to 85 per cent

of the patients operated on.[4] Our present ability to maintain normal electrolyte and fluid balance, our greater ability to combat infection, and improved surgical methods have been responsible for this.

The causes of death are usually aspiration pneumonia or separation of the suture line at the site of anastomosis of the two segments of the esophagus with resulting infection. Our experience has been that these infants usually die because the anomalous condition was not recognized early enough. Many have had pneumonia and were dehydrated by the time that they reached the hospital, the surgeon being placed at a great disadvantage if he elected to operate. There are babies who have associated anomalies which may make operation useless or impossible; however, some of them are such as to allow their correction at a later date.

I believe that all of us should profit from the discussion of this case, inasmuch as this anomaly occurs once in 2,500 to 3,000 live births.[5] If you remain in the specialty of pediatrics long enough, you are almost certain to be confronted by such a patient.

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The Interpretation of Positive Urine Cultures

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Antimicrobial drugs have provided physicians with the means to control most bacterial infections. However, problems still remain with regard to the correct identification of the causative organism and its drug sensitivities. The choice of drugs should be based, whenever possible, on these two factors. This is especially important in a disease caused by several

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different organisms, each with varying sensitivities to the antimicrobial compounds. The following paragraphs make clear the particular importance of these principles in acute and chronic pyelonephritis.

The clinical manifestations in patients with pyelonephritis are markedly varied. Such patients often present a classical picture of chills, fever, flank pain, pyuria and bacteriuria. On the other hand, particularly in infants and children, there may be none of these symptoms, but instead there is failure to gain weight, gastrointestinal disturbances or unexplained fever. In others, bacteriuria may be the only abnormality. Effective treatment in all three groups depends on a correctly interpreted urine culture. In those patients with an obvious complaint, the variety of possible organisms demands cultural evidence for the best treatment. In obscure cases, urine culture is necessary not only for treatment, but for diagnosis as well. The purpose of this paper is to discuss the major problem connected with urine culture, that of contamination by bacteria from the urethra, perineum, or from the laboratory itself.

Urine, unlike many other tissue fluids, is easily contaminated when taken for culture. Normal urethral flora, the use of unsterile catheters or containers, improper collection techniques, and delays in the laboratory handling of the culture all contribute to the frequency of contamination. The most satisfactory technique of collection of urine for culture is the clean catch, midstream specimen. This is performed in the following manner: In boys, the foreskin is retracted, the meatus cleansed with an aqueous solution of benzalkonium (Zephiran®), 1:1000, or sterile saline, and the midstream portion of the urine is taken for culture; in girls, the labia are held apart and should remain separated from the time the urethra is cleansed until the midstream specimen is collected.[1] The use of a catheter carries the risk of introducing infection into the patient.

Either method of urine collection, catheter or clean catch, may, however, result in a positive urine culture report. The physician must then make the differentiation between pathogen and contaminant. Quantitative determination of bacterial growth in the urine has proven extremely helpful in deciding whether a positive urine culture represents a true infection or contamination. This is based upon the likelihood that bacteria discharged into the urine by an infected kidney or bladder will be present in much higher concentration than normal bacterial flora (e.g. enterococci, *E. coli*) washed off the urethra into the urine, for example.

Recent studies have led several authors to arrive at the figure of 100,000 or more organisms per ml. of uncentrifuged urine as representing infection. Kass,[2, 3] working with female patients who were selected at random from an outpatient clinic and who had no clinical manifestations of a urinary tract infection, showed that bacterial counts of urine among these patients fell into two separate populations. Those who had bacterial counts between

0 and 10,000 per ml. presumably represented contamination, whereas those with more than 100,000 organisms per ml. would be expected to include women in whom actual multiplication of bacteria had occurred. It is important to note that little overlapping occurred. Kass also found that among the patients with known pyelonephritis, 95 per cent had bacterial counts in the urine of more than 100,000 organisms per ml. Other studies have also shown that patients with bacterial counts above 100,000 per ml. gave a history of urinary tract infection or past instrumentation of the urinary tract. In a recent report of female children with clinical evidence of urinary tract infection, 83 per cent had counts of 100,000 or more organisms per ml.[4] Repeat examinations disclosed 100 per cent of these patients to have counts greater than 100,000 organisms per ml. The data obtained from this study suggest that urines having less than 1000 organisms per ml. are indicative of contamination, and urines having between 1,000 and 100,000 organisms per ml. are to be suspected of infection. On the other hand, those with counts of more than 100,000 organisms per ml. are definitely indicative of infection. Sanford[5] used the figure of 10,000 to 100,000 or more organisms per ml. to distinguish true bacteriuria from contamination.

An additional simple screening procedure which correlates well with quantitative urine cultures is available and can be performed by the physician in his office. The technique is simple, and gives valuable aid to the physician in the interpretation of urine cultures. It consists of placing a loopful of the *uncentrifuged* urine on a clean glass slide over an area circumscribed with a waxed pencil mark; the use of centrifuged urine may give false positives since centrifugation will concentrate the bacteria in the sediment. The slide is then air dried, heated over a flame for fixation, and Gram stained. A positive smear correlates well with the presence of 100,000 or more organisms per ml. and a negative smear with a lesser concentration. Kass[6] reported an 80 per cent reliability of this procedure in correctly revealing the presence or absence of true baccilluria, and Berman and Reilly[7] also reported an 83 per cent reliability in 1071 urine specimens. The diagnostic importance of this procedure was cited by Pryles and Steg,[4] who reported 95 per cent reliability in children having colony counts greater than 100,000 organisms per ml.

Recently a study was undertaken at Children's Hospital to evaluate the feasibility of using quantitative urine cultures together with Gram staining as routine procedures.

MATERIALS AND METHOD

Fifty-five urine specimens taken from 50 patients were utilized in the present study. The urines were collected by clean catch or by catheter; in 5 patients, specimens were voided, without precaution, into unsterile

containers. The technique[5] used for quantitative urine cultures consisted of diluting 0.1 ml. of the uncentrifuged urine with 9.9 ml. of sterile distilled water. One tenth ml. of this mixture was pipetted into 10 ml. of liquid nutrient agar, mixed, poured into a Petri dish and allowed to harden. The dish was then incubated overnight at 37° C. The number of colonies counted by the naked eye was multiplied by 1,000 to give the number of organisms per ml. of urine. A concentration of 10,000 or more organisms per ml. was used to represent true bacteriuria. Every quantitative urine culture was accompanied by a Gram stain and a routine urine culture.

RESULTS

The use of Gram stain correctly correlated with the bacterial contamination of the urine in 82 per cent of the specimens, when 10,000 organisms per ml. was used as the dividing line. The accuracy was not significantly increased by using the figure of 100,000 organisms per ml. Table 1 illustrates the identity of pathogens and contaminants found in the present study. As would be expected, the pathogen group was dominated by *E. coli* (61 per cent). The contaminant group exhibited the wide variety of organisms found in the urethra and skin.

Clinical correlation was established by analyzing colony counts with relation to the presence of a known genitourinary tract infection, pyuria, dysuria, proteinuria or some combination of these. Ten patients with colony counts less than 10,000 organisms per ml. and 10 patients with counts greater than 10,000 organisms per ml. were analyzed. Eight in each group had clinical pictures which corresponded to the colony counts.

Table 2 illustrates the results from the five casually voided specimens. Our object was to observe the range and concentration of organisms under condition of gross contamination. Note that gross contamination invalidates the use of 10,000 or 100,000 as a dividing line; these values are to be used only with carefully taken clean catch or catheterized urines. Two of these patients had normal colony counts when repeat examinations were performed with clean catch specimens.

TABLE 1

Organisms Cultured from Urine Specimens Compared with Colony Counts Obtained

	Total	*E. coli*		Entero-coccus		Pseudo-monas		Proteus		*Staph. albus*		*Staph. aureus*	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Contaminants <10,000	28	7	25	6	21.5	1	3.5	5	18	8	28.5	1	3.5
Pathogens >10,000	13	8	61.5	3	23	2	15.5	0	0	0	0	0	0

TABLE 2

Colony Counts in Five Casually Voided Urine Samples

Patient No.	Type of Specimen	Gram Stain	Colony Count	Growth on Routine Culture
1	Routine voided	Gram-pos. cocci, Gram-neg. bacilli	100,000	*Staph. albus*, coliform org.
	Clean catch	Negative	0	*Staph. albus*
2	Routine voided	Gram-pos. cocci	100,000	*E. coli*, *Staph. aureus*
	Clean catch	Negative	0	Proteus
3	Routine voided	Gram-pos. cocci	10,000	*Staph. aureus*
4	Routine voided	Gram-neg. bacilli	100,000	*E. coli*
5	Routine voided	Negative	16,000	Enterococci

Routine urine cultures were positive in nine instances in which colony counts were less than 10,000 per ml. In the absence of quantitative urine cultures, some or all of these positive reports could have led to an erroneous diagnosis and unnecessary treatment.

COMMENT

The quantitative urine cultures obtained in these 50 patients proved to be of diagnostic value in ascertaining the presence or absence of infection. The practicality of the method was rated as excellent by the bacteriology technicians in terms of time, equipment and ease of colony counting. A concentration of 10,000 or more organisms per ml. correlated well with the presence of a genitourinary tract infection. Quantitative urine cultures were found to be feasible for use as routine procedures in conjunction with Gram stains, and frequently saved unnecessary sensitivity testing and treatment.

Results of the Gram staining correlated well with the bacterial concentration in the urine. This method offers an excellent screening procedure when carefully done.

Certain limitations to the accuracy of quantitative urine cultures should be noted. Factors which may reduce colony counts to levels below 10,000 organisms per ml. are: 1) the presence of a bacteriostatic agent in the urine of patients under treatment; 2) a urine pH of 5.0 or lower—this is bacteriostatic; 3) a rapid rate of urinary flow, which dilutes the number of bacteria in the bladder urine; 4) the presence of fastidious organisms growing poorly in the urine, e.g., enterococci; and 5) the presence of obstruction which prevents the discharge of bacteria into the urine.[6]

On the other hand, contaminated urine with originally low colony counts may yield colony counts higher than 10,000 organisms per ml. if the urine has been allowed to stand in the laboratory before plating. Refrigeration

prevents the multiplication of organisms and may be used whenever a delay is necessary.

The technical assistance of Miss Mary Elliot and Miss Jeanne Skelly is deeply appreciated.

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The Editor's Column

THE BRAIN-INJURED CHILD

The brain-injured child is a child who before, during or after birth has received an injury to, or suffered an infection of, the brain. This injury may not result in any overt neurological disability but instead in more subtle defects of motor, sensory, perceptual, emotional and integrative behavior. The brain-injured child commonly has an unpredictable variability in behavior and frequently is quite hyperactive and distractible; in a school situation, he particularly has much difficulty with subjects requiring abstract thinking, e.g., reading and arithmetic.

In 1956 a group of lay and professional people in Montgomery County, Maryland, established a nursery school for brain-damaged children. The errors of perception and thinking, and the emotional behavior peculiar to these children were recognized, and an educational program was set up with these deficiencies in mind. The results were so satisfactory that this pilot study has now been incorporated into the Montgomery County Board of Education system.

This nursery school was originally organized with six children, aged 4 to 6 years; all had previously been completely evaluated by a pediatrician, psychiatrist, and neurologist. The children attended school five days each week for a period of one and one-half hours daily. School activities were confined by very firm boundaries, and distractions of any sort were minimized; the latter is most necessary because of their easy distractibility. The problems of perception in space and eye-hand coordination were dealt with by using special toys and other materials designed by the teachers and other workers in this field.

School instruction was provided by a trained teacher assisted by four volunteers, each of whom had been given a training course by medical personnel so that he could develop an understanding of this type of affliction. Each week the parents were assembled and, under the direction of a psychologist especially trained in techniques applicable to the brain-injured child, would discuss the problems that existed at home; this was a particularly important phase of the program and one of its most gratifying aspects since it enabled progress made in school to be continued at home.

The brain-damaged child has only recently been recognized amongst our colleagues as one who can be offered a decent place in society. This is possible, however, only if these children are recognized very early in life and their special needs met by setting up an individualized and highly specific plan of management. Both parents and society are certainly unprepared for the child with this affliction; often facilities for these children are lacking and the responsibility of their education must fall on volunteer groups. It is the duty of the physician to support such programs and to see that these children are not discarded into the vast reservoir of wasted humanity. Many of these children are bright, lovable and capable of useful lives.

M. I. M.

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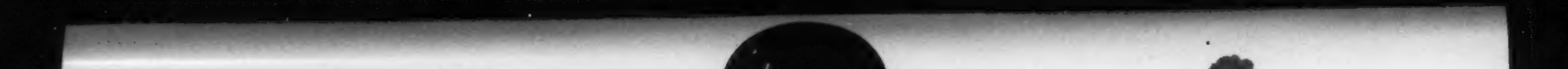
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